A Robust Absolute Structure Determination Method by Dynamical Refinement Against Electron Diffraction Data

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Absolute structure determination is an important part of the crystallographic analysis of non-centrosymmetric structures. It is especially important, particularly for biochemical and pharmaceutical applications where the absolute configuration of molecules is of great interest. The traditional method for determining absolute structure is single-crystal X-ray diffraction. However, X-ray diffraction patterns are centrosymmetric to a very good approximation, even if the structure is not. This feature of the diffraction, called Friedel's law, makes it challenging to determine absolute structure. Luckily, resonant scattering effects can break Friedel's law, making absolute structure determination from X-ray diffraction data possible. However, the strength of resonant scattering decreases with decreasing atomic number. As a result, absolute structure determination may be very challenging and sometimes impossible for crystals composed solely of very light atoms.

In recent years, 3D electron diffraction (3D ED) methods have become increasingly popular because they can provide crystallographic information from crystals many orders of magnitude smaller than those required for single-crystal X-ray diffraction [1]. However, electron diffraction data suffer from multiple scattering effects, also known as dynamical diffraction effects) that make structure analysis from them more complicated. One approach, called the kinematical refinement method, ignores dynamical diffraction effects during structure refinement, resulting in increased figures of merit, decreased accuracy of the refined structure models, and lower sensitivity to fine structural details. Alternatively, the dynamical effects can be included in the intensity calculation during the structure refinement. This approach, called dynamical refinement, usually provides lower figures of merit and more accurate structure models [2,3] but requires longer computing time and high-quality diffraction data.

Dynamical diffraction effects are generally considered a nuisance in 3D ED methods, because they prevent obtaining accurate results with the kinematical approach. However, dynamical effects also have one useful property: they break Friedel's law. Hence, it is possible to determine the absolute structure by exploiting the dynamical effects [3,4]. The effect behind breaking the Friedel's law is not resonant scattering, but multi-beam interference. As a result, the strength of the breaking of Friedel's law is not dependent on the atomic number, and is equally strong for structures composed of heavy as well as light elements. The effect is also significantly stronger than the breaking of the Friedel's law by resonant scattering in x-ray diffraction.

In practice, the effect is strong enough to distinguish easily between correct and wrong enantiomorphs by refining both candidates against experimental data and comparing the refinement R-factors. In some cases, the difference can be as high as 10 percentage points, and in most cases, it is higher than 1.5 percentage points. The reliability of the determination of absolute structure can also be expressed quantitatively, using a method by Le Page et al. [5] modified for 3D ED data [3]. The reliability can be expressed as a z- score, representing a sigma-level of confidence. Z-scores in the range of 3-10 σ are usually obtained, indicating very good reliability of the absolute structure determination.

The method was tested on over a hundred individual datasets, including a large number of datasets publicly available on the data repository zenodo.org, and has proven effective in almost all of them. At present, the method works only for materials that are known to be enantiomerically pure, but a generalization of the method for reliable absolute structure determination in cases of possible presence of an inversion twinning is under development.

References:
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